Children who have a general respiratory tract infection, with only a moderate laryngeal obstruction which is worse at night and subsides during the day, in most cases can be safely treated as having common croup. But where diphtheria is proven or is likely, large amounts of intravenous antitoxin, warmed, diluted and given slowly are indicated. We have given fifty to one hundred thousand units in several cases with recovery where instrumentation seemed unavoidable at the onset.

Active immunization of our child populace against diphtheria has materially reduced the incidence of laryngeal obstruction, but unfortunately only a very small number of those immunized are followed up with Schick tests to determine immunity.

When in doubt as to the pathology present or the course to pursue in treatment, no time should be wasted in calling the laryngologist.

❦

Barton J. Powell, Jr., M. D. (Medico-Dental Building, Stockton).—Fortunately for humanity, cases of laryngeal obstruction in children are becoming less and less frequent. The greatest single cause of this reduction is undoubtedly the early use of antitoxin therapy and prophylactic treatment of diphtheria. This disease is fast becoming an uncommon entity and the severity of those cases which do appear is usually attenuated. As Doctor Tillotson has brought out, direct laryngoscopic examination of all cases of laryngeal diphtheria with asphyxia should be done. By this procedure the exact condition of the structures can be noted, smears taken direct from the laryngeal mucosa and intubation readily accomplished. Intubation by direct laryngoscopy affords a quicker and surer method and will, I believe, supplant the older methods where the field of operation is hidden from view.

A frequent cause of acute laryngeal obstruction in children is the inspiration of foreign bodies. These usually demand immediate action. A foreign body on the aryteno-epiglottic folds, or even in the cavity of the larynx, can often be dislodged with the finger and the patient subsequently expel it by coughing. Care must be taken with this procedure not to force the material through the glottis. In cases where the obstruction is partial and asphyxia is not impending, direct laryngoscopy should be done and the foreign body removed with the laryngeal forceps. Where time and opportunity permits, roentgenograms are often helpful in locating the object.

Doctor Tillotson has stressed the indications and advantages of tracheotomy and I wish to again emphasize the importance of this life-saving procedure. The operation is neither difficult nor serious. There is little operative trauma, and complications are rare. Tracheotomy should be done in every case where asphyxia is impending and where the less radical procedures do not immediately supply the required relief. This excellent operation is only too often regarded as a last-moment attempt to ward off exitus. When the indications are present, perform tracheotomy immediately. Do not wait until the patient is in extremis and thereby severely jeopardize a favorable prognosis.

❦

Orrin S. Cook, M. D. (Medico-Dental Building, Sacramento.)—Fortunately or unfortunately the roentgenologist has the opportunity of seeing very few cases of laryngeal obstruction. Most of these cases are acute and are diagnosed without waiting for an x-ray examination. Most of the patients whom we see are those where foreign bodies lodge in the larynx. This is comparatively rare, but occasionally does happen. If the foreign bodies are radio-opaque, the x-ray is of considerable assistance, but if they are radio-lucent the x-ray does not help.

The only other condition which I have seen with any frequency is retropharyngeal abscess. This condition in the advanced stages gives a bulging of the posterior wall of the pharynx in the lateral view which is quite diagnostic.

❦

Doctor Tillotson (Closing).—I have endeavored in this paper to stress the cardinal signs of laryngeal obstruction and point out the measures at our disposal in determining its cause. The procedures employed in maintaining a patent airway in this portion of the respiratory tract have been given. I agree with Doctor Powell that the operation of tracheotomy is not difficult or serious, with the qualification that the incision in the trachea should always be made below the first tracheal ring, avoiding injury to the cricoid cartilage. Injury to this cartilage may result in chronic laryngeal stenosis. After-care in keeping the tracheotomy tube and trachea clean, using suction if necessary, is of the greatest importance in avoiding post-tracheotomy complications.

BACTERIOPHAGE AS A THERAPEUTIC AGENT IN GENITO-URINARY INFECTIONS*

By E. W. Schultz, M. D.
Stanford University

INTRODUCTION

WILL ROGERS claims that all he knows is what he reads in the newspapers. All I can claim to know regarding the therapeutic merits of bacteriophage in genito-urinary infections is what I have read in the clinical reports sent to my laboratory. Whether the source of my information is any more reliable than that of Will Rogers' is problematic. Despite this uncertain status of my knowledge your program committee has had the courage to invite me to dispense something more or less authoritative on a singularly intricate question—has bacteriophage a place among therapeutic agents of value to the urologist? I must admit at once that I have failed to bring you a categorical answer to this question. To some this may represent the equivalent of a negative reply, but this is not necessarily the case. With any therapeutic procedure which does not yield uniformly successful results—and these are rare—one should not allow himself to be led astray by the failures which may initiate or sprinkle an inquiry. A procedure may have inherent merits, but these may not be fully revealed until the various factors which influence the result have been determined and, if possible, brought under control. Though we recognize that Nature yields up her secrets with great reluctance, we are often apt to draw conclusions long before the evidence is in. Indeed, some of us find the path a little too irksome and are inclined to seek a way out in logic whatever the original premises may perchance happen to be. We cannot escape the fact, however, that, while people may argue indefinitely (as it is said they once did) as to

*From the department of bacteriology and experimental pathology, Stanford University, California.

*Read before the Western Branch of the American Urological Association, November 6, 1931.

whether or not a fish when put into a full bowl of water will cause water to flow out of the bowl, the only way to really settle such a question is to actually put a fish into the bowl and observe the results.

HOW THIS STUDY AROSE

Several years ago, during a period of a great discussion for and against the possible merits of bacteriophage as a therapeutic agent, it occurred to us that a more satisfactory way to settle this question might be to provide a special service which would enable interested physicians to determine by *actual trial* the therapeutic merits of this agent. It was obvious that the commercial products which were beginning to appear on the market would not be likely to clear the atmosphere. It was clearly apparent from a review of the literature that only the most suitable 'phages for each individual case should be provided to the physicians actually on the firing line of such an investigation. The physicians using the service which we inaugurated have reported their results to us, and it is to these clinical reports that I shall refer in this paper.

THE PHENOMENON OF BACTERIOPHAGY

We find that there still are some physicians to whom bacteriophagy is either an essentially unknown phenomenon or regarding which they have very fragmentary knowledge. This may seem a little surprising in view of the fact that nearly twelve hundred papers have appeared in biologic and medical literature bearing on various aspects of the phenomenon, but it may not be generally known that very good reviews,[1] presented from different viewpoints, are now available in both American and British literature for the benefit of the English reader, not to mention some of the briefer reviews which accompany some of the clinical reports. Since there is still some haziness regarding the essential features of this phenomenon, a brief survey may be welcome before we take up an analysis of the clinical results.

The phenomenon of bacteriophagy may be defined as the lysis of bacteria by an infravisible agent of unknown nature, regenerated at the expense of the bacteria dissolved under its action. The lytic principle itself (bacteriophage) is often referred to as *transmissible bacterial lysin* for the reason that it may be distinguished from all other bacteriolytic agents by the fact that it is regenerated and increased during the progress of bacterial lysis, a drop of one dissolved culture being all that is necessary to initiate dissolution of the next. In a series of any length the culture finally dissolved will present about the same concentration of bacteriophage as the original filtrate, provided, of course, that suitable conditions for bacterial growth and multiplication are offered. An interesting aspect of the phenomenon is that young growing cultures seem to be necessary for its normal progress. Indeed, once added to a young culture, bacteriophage gives impetus to bacterial proliferation, causing the young, already rapidly dividing cells, to be plunged into an orgy of reproductive activity. During this active bacterial proliferation, individual cells begin to swell and rupture in an explosive manner. With rapidly increasing momentum more and more organisms disappear in this manner, with the result that in the course of a few hours after the onset of the phenomenon a highly turbid broth culture may become entirely clear and essentially free of organisms. Since bacteriophage exercises a growth-stimulating action on young cultures followed by an explosive rupture of individual organisms, the result of a sudden influx of water into the cell, certain investigators have concluded that bacteriophage may be an enzymic principle acting in some way on the surface membrane of bacteria, causing a sudden influx of water, resulting in an explosive rupture of the cell. On such an assumption one might define *bacteriophage* as a malign influence which plunges bacteria to an early death as a result of *"fast living"* and *"too much drinking."*

What the precise nature is of the agent responsible still remains a mystery. Not a few theories have been advanced in explanation, but, unfortunately, not one of them can be said to have the support of *all* the facts. So far as its possible usefulness as a therapeutic agent is concerned, it matters little whether the agent is a living virus; a ferment elaborated by tainted microbes, or of some other nature. The important fact is that it is a transmissible lysin which impresses itself on susceptible organisms. I say "susceptible organisms" because bacteriophages capable of attacking some organisms are often entirely unable to impress themselves on others. Indeed, a 'phage active for a given bacterial species is frequently entirely incapable of attacking some of the strains of that particular species. 'Phages differ widely in this respect. Some may possess a very wide range of activity, spreading their activity over several bacterial species, while others may restrict their activity to a single strain or two of a given species. This difference in range of activity represents one of the chief stumbling blocks in an inquiry designed to elicit the value of bacteriophage as a therapeutic agent. Without preliminary laboratory tests it is impossible to say whether or not a given 'phage will lyse, even in the culture tube, an organism responsible for a given infection. While it is possible by the selection and pooling of an adequate number of different 'phages to somewhat overcome these uncertainties, it is obviously impossible to study the therapeutic merits of bacteriophage without definite knowledge that the causal organism is lysable *in vitro*.

Not only do 'phages differ in the range of their activity, but they differ widely in the intensity and completeness with which they effect lysis. While the differences which may be exhibited is not wholly a function of the 'phage, but of the organisms as well, the selection of more active "virulent" 'phages for therapeutic studies is, nevertheless, exceedingly important. The ideal 'phage for therapeutic trial is obviously one which

1 d'Herelle, 1926, 1930; Brugnoghe, 1927; Hadley, 1928; Schultz, 1929, 1930; Twort, 1930; Burnet, 1930.

not only causes complete lysis of the cultures of the causal bacterium, but one which tends to hold in check the appearance of the so-called *secondary cultures*. Such 'phages, however, are the exception rather than the rule, and this is particularly true of 'phages active for the colon group of organisms. With these organisms, secondary 'phage-resistant variants almost invariably make their appearance in unfiltered lysed cultures within twenty-four to forty-eight hours after maximum lysis, especially if optimum temperature conditions prevail. There are, on the other hand, instances in which unfiltered cultures remain clear for days, and even for weeks. We have, for example, in our possession a staphylococcus bacteriophage which generally holds the appearance of secondary cultures in check for longer periods of time. Lysed coli cultures, as I have indicated, generally show secondary cultures promptly, unless kept at low temperatures (15 to 20 centigrade). This tendency for 'phage-resistant variants to arise is not without bearing on the results of 'phage therapy. It should be added, however, that the appearance of 'phage-resistant organism in the tissues of the affected host does not mean that the patient is left with a more virulent infection. On the contrary, these 'phage-resistant variants are generally distinctly less virulent in character. During the past few years a great deal of work has been reported on the subject of *bacterial variation*. It has been found that cultures of most pathogens may naturally shift from the so-called "S," or smooth, more virulent types, to the "R," or rough types, which relatively are avirulent; the "smooth" forms giving rise to stormy, the "rough" forms to less stormy clinical pictures. I shall refer to this again later.

Bacteriophages have been isolated for many different species of bacteria, including members of the colon typhoid-dysentery group; the hemorrhagic septicemia group; the diphtheria and diphtheroid group; for the pyogenic cocci and many nonpathogens. For some of these it is much more difficult to find 'phages than for others. It is not difficult to find 'phages for members of the colon group, but very difficult to isolate those active for staphylococci, and especially for streptococci. While we have experienced no great difficulty in isolating 'phages active for various nonhemolytic streptococci, in only a few instances have we been fortunate enough to recover those active for hemolytic streptococci. This seems to have been the experience of other investigators, for there is scant reference to streptococcus 'phages in the literature. Contrary to the experience of other investigators we are able to lyse hemolytic as well as nonhemolytic variants of *Staphylococcus aureus*.

The sources of 'phages are varied. The feces of man and animals; normal, diseased, and convalescent, present 'phages in varying quantities and of different ranges and degrees of activity. The most commonly used source is sewage; the sewage of large cities being more promising than that of smaller towns. Healing wounds offer another source, as do also nasopharyngeal washings: sources which should in reality be studied more carefully, especially for 'phages active for the pyogenic cocci. The urine from cases suffering with chronic cystitis may, as Larkum (1926) and others have shown, frequently contains a bacteriophage of weak or moderate activity. Sewage has the advantage in that it contains a rich mixture of 'phages, all of which may be revealed if we take the trouble to test the sewage filtrate simultaneously against a sufficiently large number of bacterial species and strains. Recently we have begun the practice of feeding bacterial strains which we have been unable to lyse to various animals, including the horse, rabbit, dog, chicken, duck, and monkey, with, in the main, gratifying results. It is evident from what I have just said regarding the sources of 'phage that we do not, as some physicians seem to believe, "develop a bacteriophage from the cultures" sent us. There is no convincing evidence to support the view that bacteriophage may be developed from an originally 'phage-free culture.

LITERATURE ON BACTERIOPHAGE THERAPY

Those who are familiar with the basic aspects of the Twort-d'Herelle phenomenon find no difficulty in understanding why investigators quite early in the development of this new knowledge began to ask themselves why such an agent should not possess therapeutic merits. On theoretic grounds at least, bacteriophage possesses all the features of an ideal therapeutic agent, not only in being potentially able to destroy the causal agent, in the process of which it is regenerated, but in being at the same time, so far as all evidence goes, entirely harmless to the patient. For what other therapeutic agents may as much be said? With most therapeutic agents the germicidal activity *in vivo* must always be carefully weighed against the depressing, and even more damaging action, which they may exercise on tissues already the seat of more or less marked microbic injury. To say, however, that bacteriophage possesses, theoretically at least, the properties of an ideal therapeutic agent still leaves its actual practical usefulness an open question. An agent may be wonderfully effective as a germicidal agent in the test tube and at the same time prove relatively inert when applied against the same organism within the confines of an infected tissue. The actual proof must, therefore, always rest in the last analysis on careful clinical studies. In the case of bacteriophage there is, unfortunately, a relative dearth of significant clinical observations. While there are a number of reports in the literature bearing on its use in urinary infections, the individual series are for the most part small and not altogether satisfying. One gathers the general impression, however, from the great majority of the reports relating to the treatment of urinary infections by 'phage [2] that when

[2] Becherich and Hauduroy, 1922, 1923; Couroux, Philibert and Cordey, 1922; Alphonsi, 1924; Arloing, Dufour, Bouvier and Sempé, 1924; Philibert, 1924; Pereira, 1924; Lehndorff, 1924; Zdansky, 1924, 1925; Frisch, 1925; Dalsace, 1926; Larkum, 1926; Cowie, 1926; Sickenga, 1925; Caldwell, 1928; Krueger, Faber, and Schultz, 1930.

properly chosen and properly administered the 'phage possesses well-defined therapeutic merits in the less complicated types of pyelocystitis. These results, together with the generally favorable trend of the reports bearing on the treatment of nonurinary infections such as furunculosis, carbuncles, and wound infections due to staphylococcus,[3] all seem to argue clearly for at least a further investigation as to its usefulness as a therapeutic agent.

RESULTS REPORTED TO OUR LABORATORY

A. *Bacillus coli, Pyelitis, and Cystitis:*

May I summarize now the clinical results which have been reported to us by physicians to whom 'phages have been supplied by our laboratory. The analysis of these reports has been far from a simple and altogether satisfying task, mainly for the following reasons, which I should like to unburden myself of at this time. Though we have endeavored to make clear to physicians using our laboratory service that our part in this coöperative endeavor is prompted solely by a desire for reliable information as to the therapeutic merits of bacteriophage, it has proven exceedingly difficult to secure the type of reports needed in a study of this sort. The following represent a few of the more common faults in rendering reports: (1) failure to give a complete clinical diagnosis. Indication as to whether pyelitis is *acute* or *chronic* is of far greater importance in a study such as this than information that the infection is on the right or left side; (2) failure to give a synopsis of the clinical history. This is especially important when the diagnosis is entirely omitted; (3) I believe you will grant that in a therapeutic study the size of the dose administered, the route, and the spacing of the doses should be carefully entered in a report, and yet, such pertinent information is not infrequently omitted from these reports; (4) the results realized by the treatment certainly deserve some comment, but this is also sometimes omitted. I should state, parenthetically, that in our directions on the report blank we have requested that clinical results be reported as "positive" only when there *seemed* to be no doubt as to relationship of the clinical improvement to the therapeutic procedure. One can, of course, never be certain that in the individual case the two are always directly related, but some significance can probably be attached to such observations when they relate to a sufficiently large number of cases. *Doubtful* as well as clearly unchanged clinical conditions we have asked the physicians to report as "negative."

Now, what do the reports on treatment of pyelitis and cystitis show? After discarding the incomplete records, there remained for analysis a total of 191 case reports; 40 of these relate to acute and subacute cases, and 151 to chronic cases. Let me reverse the order and present first the results reported on the chronic cases. Of the 151 cases in this series 72 were reported as "positive," while 79 were reported as clearly unchanged or "negative." That is, of the total number of chronic cases treated, approximately 47 per cent were thought to have been improved by 'phage treatment. Of this number, fifteen recurred *within* a period of ten days; one recurred after two weeks, and one after three months. It is possible that more than two recurred after the tenth day, but my information on this point is lacking. It is noteworthy that of the seventy-two cases which were recorded as having been improved, thirteen seem not to have become entirely free of the colon organism in the urine at any time, though in the minds of the physicians reporting these cases there was unquestionable clinical improvement immediately following the treatments; an improvement which, so far as my information goes, persisted for some time. In the light of our present-day knowledge regarding bacterial variation, either induced by 'phage or occurring naturally, such a therapeutic effect is not improbable. In such instances there is presumably a shift from the more virulent "S" type to the less virulent "R" type variants (Hadley, 1928). Returning to the case reports, if we now count out the cases which suffered recurrences, likewise those in which the organisms persisted in the face of clinical improvement, there remain in this series forty-two cases, or 28 per cent of the entire series of 151 chronic cases, regarding which there is, so far as I can ascertain, no question as to the immediate and apparently complete response to the treatment. Thirty-two of this number cleared up within forty-eight hours after the first dose of 'phage was administered; the remaining ten responding within seventy-two hours. Unfortunately, I have comparatively little information regarding associated anatomic disturbances in this particular group, but it appears that, with the exception of two cases of renal ptosis and two of prostatitis, the series seems to have been essentially free of more significant anatomic disturbances. However, in the series of seventy-nine cases which failed entirely to respond, associated pathologic states were indicated in the diagnosis or clinical histories of a fair number, and these complications included prostatitis, prostatic hypertrophy, epididymitis, renal ptosis, hydroureter, ureteral stricture, ureteral obstruction, renal and bladder calculi, pyelonephritis, diverticulum of the bladder, leukoplakia of the bladder, neurological bladder, renal tuberculosis, actinomycosis, metastatic cancer, etc. Quite apart from the question as to whether the 'phage would have precipitated recovery had the anatomic status of these cases been less abnormal, it seems scarcely proper to include cases of this type in a basic inquiry of this sort. I have gathered the impression that the bulk of the cultures we receive for 'phage susceptibility test are from cases which are more or less exasperating to physicians who in

[3] Bruynoghne and Maisin, 1921; Gratia, 1922; Sauvé and Jacquemaire, 1929; Raiga, 1929; Bazy, 1925; Larkum, 1928; Rozemon, 1929; Alderson, 1930; Crutchfield and Stout, 1930; Sauvé, 1930; as in the treatment of dysentery (d'Herelle, 1921; da Costa Cruz, 1924; Pereira, 1924; Spence and McKinley, 1924; etc.); typhoid and paratyphoid infections (Beckerich and Hauduroy, 1922; Hauduroy and Arsimoles, 1923; Hauduroy, 1925; Alessandrini and Doria, 1924; Smith, 1924; Richet, Azerad and Delarne, 1924; Breton, 1930; etc.

final desperation have said to themselves, "Well, now isn't this a case on which to test the therapeutic merits of 'phage?" This is a perfectly natural reaction, but is this the type of case on which to base such an inquiry? A sounder practice would seem to be to give alternate cases 'phage, and then compare the results with other forms of therapy.

(To be continued)

TETANUS*

By JOHN E. WRIGHT, F. R. C. S.
Reno, Nevada

THE tetanus bacillus is widely distributed throughout the world, but is more common in certain districts than others. It is very common in the tropics and in some of the tropical islands, where the temperature remains constantly fairly high, and under these conditions appears to possess an increased virulence. It occurs normally in the intestines of herbivora and to a lesser extent of other animals and man. It is found in 15 per cent of horses around New York. For this reason highly cultivated manured districts frequently contain the bacilli and spores in large numbers. The spores are extremely resistant, both to heat and chemicals, and can retain their vitality for years in a dry condition. By means of an infected splinter, Henrijean reports a successful animal inoculation after eleven years. It produces exotoxins, tetanospasmin and tetanolysin, the former with a special affinity for nerve cells, probably related to their lipoidal contents, the latter of little pathological importance. Susceptibility in different animals varies enormously. The amount of toxin sufficient to kill a fowl will kill five hundred horses. Under natural conditions fowls do not contract the disease, while horses under their extreme susceptibility are especially liable to contract tetanus following any wound. Man is almost as susceptible as the horse, and to him 1/300 of a grain of the toxin is a fatal dose.

Deep, contused and badly lacerated wounds, especially if a foreign body is present, are favorable but by no means the invariable accompaniment of infection. I have seen more than one case develop through feet infected with chiggers. The bacilli tend to remain localized to the point of infection and there multiply moderately and produce their exotoxin, which is taken up by the end plates of the motor nerves and travels by the axis cylinder to the central nervous system. A few may be transported by leukocytes.

The incubation period varies within wide limits, roughly from five days to three weeks, usually from ten to fourteen days. That is the time taken for the toxin to travel from the point of infection to the central nervous system. Symptoms appear earlier in tropical countries, sometimes within a few hours. The shorter the incubation period the worse the prognosis.

* From the Holberton Hospital, Antigua, British West Indies.

* Abstract of an address given before the Washoe County Medical Society of Nevada on June 9, 1931.

SYMPTOMS

The early symptoms are rather indefinite, but restlessness, irritability, insomnia, and sleep broken by terrifying dreams frequently occur. The existence of slight muscular rigidity or twitchings in the neighborhood of a suppurating wound should arouse suspicion and this is usually coupled with an exaggerated reflex response to gentle tapping of the muscles of the limb. Cases of local tetanus not infrequently occur on opening up and operating on old war injuries.

There may or may not be a peculiar grin, known as the risus sardonicus. The spasms spread to the trunk and limbs, which are exceedingly painful, violent, and exhausting, with only partial remissions; the patients usually remain quiet, probably from fear of provoking spasms. Fortunately the respiratory muscles are involved late. The slightest stimulus, *e. g.,* a draught, attempt at voluntary movement, or a banging door, is sufficient to throw the victim into violent spasms of a tonic character. The body is contorted and the respiration impeded with grunting and, indeed, muscles may be ruptured by the violence of the contractions on occasions.

A general rigidity, statuesque, is commonest in my experience, but an arching backwards of the spine (opisthotonus) is also common. Temperature usually runs from 101 to 103 degrees, but hyperpyrexia is not unusual. A moderate leukocytosis of 12,000 to 14,000 with a polymorphonuclear count of from 80 to 90 is the general rule. The unfortunate individual is only too conscious of his pitiable plight, shown by the look of terror which to me is almost characteristic. Death usually occurs in fatal cases in from three to five days from exhaustion.

Prognosis.—The prognosis is always serious. In cases in which symptoms show themselves under ten days it is about 40 per cent, but after three weeks it drops to about 15 per cent. Too often the disease is fully developed before treatment is commenced. Signs of bad prognostic import are hyperpyrexia, sleeplessness, strabismus, dysphagia, and respiratory involvement.

Diagnosis.—The most reliable test is to dilute some of the discharge from the deep parts of the wound with broth, divide it and inject one part into a susceptible animal, like a mouse or a guinea-pig, while the other is mixed with one cubic centimeter of tetanus antitoxin and injected into another animal. If the former develops tetanus while the latter escapes, there should be no doubt as to the diagnosis. Do not wait to establish a diagnosis in a doubtful case.

TREATMENT

In treatment the first and most important factor is to give a prophylactic dose of 1500 units to every case where a wound or injury may be suspected of harboring the bacillus, such as blank cartridge wounds, and wounds likely to be contaminated with soil or manure. If there are reasonable grounds for suspicion this dosage should be repeated at the end of a week or ten days. Subcutaneously, antitoxin is absorbed